whereas the phenyl rings of the diphenylvinylidene group make an angle of 53°.

Tetra-p-anisylbutatriene (II) is dimorphic (A,B).[15] Both modifications yield the same photoproduct, form B reacting faster. V has mp 293°: M+ 952, strong peak at M/2 476; nmr a multiplet centered at τ 3.1 (aromatic protons) and two singlets at 6.23 and 6.18 (OCH₃), which do not coalesce on heating above 150° in DMSO; ν_{max} Raman 1960 cm⁻¹(s) (alenic group). These physical data together with the match in cell constants of the dimers IV and V,[16] strongly indicate that V is 1,3-bis(di-p-anisylvinylidene)-2,2,4,4-tetra-p-anisylcyclobutane.

These results suggest that the solid-state photodimerizations of cumulenes may differ from thermal cycloaddition reactions which take place via the central C=C bond to form radialenes.[17]

The X-ray analysis of I as well as the photochemical studies of other tetraarylbutatrienes, presently in progress, will be reported in a full paper.

Acknowledgments. We thank Dr. V. Zaretzky and Dr. F. Nader for the mass spectra, Dr. E. Huler for the Raman spectra, and Professor M. D. Cohen for helpful discussions. Partial support from a Minerva Grant is also acknowledged.

(15) Form A, ex ethyl methyl ketone, chloroform, chloroform-ethanol: triclinic; $a = 9.8, b = 11.7, c = 10.9$ Å; $\alpha = 96.5, \beta = 103.0, \gamma = 87.1°$; $Z = 2$; $\rho_{calcd} = 1.31$. Form B, ex benzene, single crystal suitable for cell constant determination not obtained.
(16) Cell constants of V: triclinic; $a = 10.5, b = 21.6, c = 11.8$ Å; $\alpha = 100.2, \beta = 101.3, \gamma = 88.0°$; $Z = 2$; $\rho_{calcd} = 1.2$.
(17) H. D. Hartzler, J. Amer. Chem. Soc., 88, 3155 (1966); B. Heinrich and A. Roeding, Angew. Chem., Int. Ed. Engl., 7, 375 (1968).

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Total Synthesis of Dihydrostreptomycin

Sir:

Streptomycin is the first useful *Streptomyces* antibiotic discovered by Waksman and coworkers[1] in 1943. Dihydrostreptomycin[2,3] is obtained by hydrogenation of streptomycin or by direct fermentation.[4] The structure of streptomycin was established by 1948 except for the glycosidic linkage between streptose and

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streptidine which was again revised[5,6] to be α-L. We wish here to report the total synthesis of dihydrostreptomycin. This represents the first synthesis of an antibiotic of the streptomycin series.

Condensation of the blocked derivative[7] (1) of dihydrostreptose[8] with the L-glucosamine[9] derivative[10] (2) in benzene in the presence of mercuric cyanide at room temperature, followed by hydrolysis of the Schiff base with 50% acetic acid and reaction with methyl chloroformate (Na₂CO₃, aq acetone), gave the disaccharide 3 in 42% overall yield from 1: $[\alpha]^{24}D$ −133° (c 0.8, CHCl₃). N-Methylation (MeI, Ag₂O, DMF) gave 4 (72%). Deacetylation (MeONa–MeOH) followed

1

2

3, R = H
4, R = Me
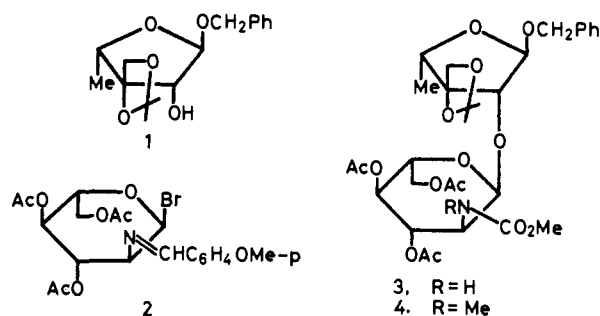
by deisopropylidenation (1 N HCl, aqueous MeOH) gave 5 (70% yield from 4; mp 184.5–185°; $[\alpha]^{18}D$ −153° (c 2, MeOH)), which was identical with the natural specimen derived from benzyl α-L-dihydrostreptobiosaminide[11] similarly with methyl chloroformate. Hydrolysis of 5 (10% Ba(OH)₂, 70°, 72%) afforded benzyl α-L-dihydrostreptobiosaminide (6).

Treatment of 6 with 2,2-dimethoxypropane (p-toluenesulfonic acid, molecular sieve type 5A, acetone, reflux, 69%) gave a diisopropylidene derivative, and further blocking by use[12] of p-nitrophenoxycarbonyl chloride (NaOH, aqueous acetone, −10°, 75%) gave 7: $[\alpha]^{23}D$ −152° (c 1, MeOH); ir 1770 cm⁻¹

5, R = CO₂Me
6, R = H

7
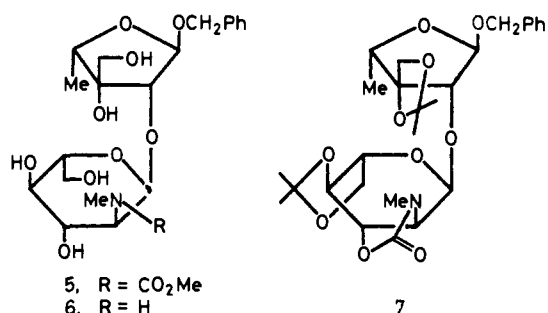
(5) I. J. McGilveray and K. L. Rinehart, Jr., J. Amer. Chem. Soc., 87, 4003 (1965).
(6) S. Neidle, D. Rogers, and M. B. Hursthouse, Tetrahedron Lett., 4725 (1968).
(7) Compound 1, benzyl α-L-dihydrostreptoside ($[\alpha]^{25}D$ −100° (c 1, CHCl₃)), prepared from dihydrostreptose,⁸ was treated with 2,2-dimethoxypropane and p-toluenesulfonic acid in DMF to give 1 $[\alpha]^{18}D$ −85° (c 1, CHCl₃).
(8) J. R. Dyer, W. E. McGonigal, and K. C. Rice, J. Amer. Chem. Soc., 87, 654 (1965).
(9) R. Kuhn and W. Kirschenlohr, Justus Liebigs Ann. Chem., 600, 115 (1956).
(10) Compound 2, L-glucosamine,⁹ was treated with p-anisaldehyde. The resulting Schiff base was acetylated and followed by treatment with hydrogen bromide–acetic acid in methylene chloride to give 2 in 30% overall yield: mp 110–111°; $[\alpha]^{20}D$ −194° (c 1, CHCl₃).
(11) G. K. J. Ferguson, I. J. McGilveray, and J. B. Stenlake, J. Pharm. Pharmacol., 17, Suppl. 68S–70S (1965).
(12) S. Umezawa, Y. Takagi, and T. Tsuchiya, Bull. Chem. Soc. Jap., 44, 1411 (1971).

(cyclic carbamate). Partial hydrolysis of 7 (25% AcOH in MeOH, reflux) gave the diol 8 (95%): mp 190–190.5°; $[\alpha]^{23}$D −177° (c 1, MeOH). This was converted (PhCOCl–pyridine, 91%) into the dibenzoyl derivative 9: $[\alpha]^{18}$D −145° (c 1, CHCl₃). Partial hydrolysis (75% AcOH, 70° 83%) removed the isopropylidene group, giving a diol, $[\alpha]^{18}$D −177° (c 1, CHCl₃), which was transformed (p-NO₂C₆H₄-OCOCl, pyridine) into the carbonate 10 (91%): $[\alpha]^{18}$D −145° (c 1, CHCl₃); ir ($\nu_{C=O}$) 1815 (carbonate), 1775 (cyclic carbamate), 1725 cm⁻¹ (ester). Hydrogenolysis of the glycosidic linkage (Palladium Black, dioxane, 99%) gave the free sugar 11: $[\alpha]^{18}$D −95° (c 1, CHCl₃). Reaction with thionyl chloride at room temperature afforded the α-glycosyl chloride 12 in

8, R = H
9, R = COPh
10, R = OCH₂Ph (α-anomeric)
11, R = OH
12, R = Cl (α-anomeric)
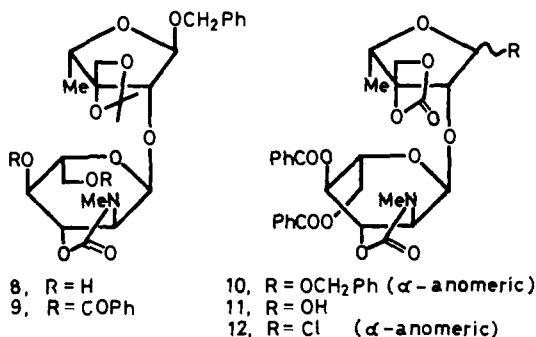
77% yield.[13]

Direct treatment of 6 with p-nitrophenoxycarbonyl chloride or phosgene followed by benzoylation gave a poor yield of 10. Transformation of 9 into a chloride corresponding to 12 by similar hydrogenolysis followed by chlorination was avoided, because the authors observed that transketalization occurred in the chlorination of 2-O-acetyl-3,3′-O-isopropylidenedihydrostreptose with thionyl chloride.

Finally, condensation of 12 with di-N-acetyl-di-N-benzyloxycarbonyl-O-cyclohexylidenestreptidine[14] (13) (Ag₂CO₃–AgClO₄, molecular sieve type 3A, benzene, 50°) gave four condensation products and one of them having $[\alpha]^{25}$D −70° (c 2, CHCl₃) proved to be the 4-O-glycoside[16] 14 (10%). Hydrolysis (0.05 N Ba(OH)₂, dioxane, 60°) selectively removed the carbamate, carbonate, benzoyl, and acetyl groups to give a di-N-benzyloxycarbonyl-O-cyclohexylidene derivative (73%), $[\alpha]^{28}$D −63° (c 1, MeOH). Removal of the remaining

(13) Compound 12: mp 114–116°; $[\alpha]^{18}$D −170° (c 1, CHCl₃); ir 1820, 1770, 1725 cm⁻¹; pmr (CDCl₃) δ 1.26 (d, 3, CHCH₃), 2.94 (s, 3, NCH₃), 5.32 (d, J = 3 Hz, H-1′), 6.33 (d, J = 1.5 Hz, H-1).
(14) Compound 13; reaction of streptidine[15] with excess benzyloxycarbonyl chloride and 2 N NaOH in aqueous dioxane followed by partial hydrolysis with 2 N NaOH in dioxane gave di-N-benzyloxycarbonylstreptidine (50%), which, by treatment with 3,4-dihydro-2H-pyran and p-toluenesulfonic acid in DMF, gave a tetra-O-tetrahydropyranyl derivative (70%). Acetylation with acetic anhydride–pyridine containing triethylamine then gave a di-N-acetyl derivative (98%), which, by removal of the tetrahydropyranyl group by acid hydrolysis followed by reaction with 1,1-dimethoxycyclohexane, led to 13 (racemate, 40%), mp 117–118°, which is satisfactorily soluble in benzene. The positions of acetyl and benzyloxycarbonyl groups attached to nitrogen are arbitrary and the assignment is under study. This is the first preparation of a useful intermediate for the synthesis of streptidine glycosides.
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(16) Compound 14 was isolated by silica gel chromatography with C₆H₆–CHCl₃–EtOH–concentrated NH₄OH (50:50:4:0.5) and C₆H₆–90% EtOH (25:1); ir ($\nu_{C=O}$) 1810, 1775, 1725, 1640, 1570 cm⁻¹; pmr (CDCl₃) δ 1.30 (d, 3, CHCH₃), 2.18 (s, 6, Ac), 2.94 (s, 3, NCH₃), 7.40 (s, 10, CH₂Ph), 7.4 and 8.1 (br, 6 and 4, respectively, COPh).
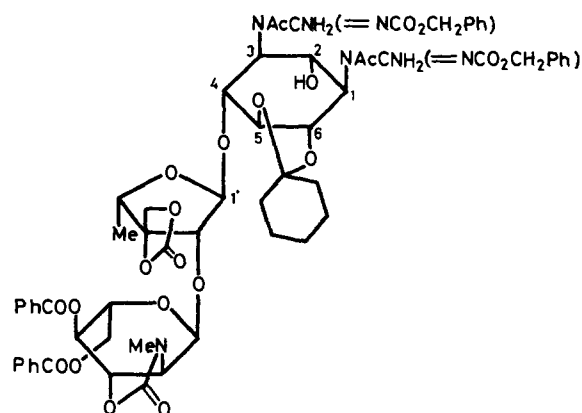
14

protecting groups with 50% acetic acid and hydrogenolysis with Palladium Black afforded dihydrostreptomycin[17,18] (60% as sesquisulfate; $[\alpha]^{25}$D −88° (c 0.1, H₂O), identical[19] with a natural specimen in optical rotation; ir and pmr spectra (in D₂O, H-1′ had J = 1.3 Hz)). The C-4 glycosidic linkage was confirmed by the $\Delta[M]^{10}_{436(CuAm)}$ value[20] (−1200°) identical with that of natural dihydrostreptomycin.

(17) See ref 5 for the structure of dihydrostreptomycin.
(18) After submission of the manuscript, dihydrostreptomycin has been converted into streptomycin by oxidation with Me₂SO–DCC followed by chromatographic separation.
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Photochemistry of Methyl Diazoacetate in Chloromethanes Studied by CIDNP

Sir:

In sharp contrast with the photolysis of diazomethane, a radical chain mechanism was considered a remote possibility in the reactions of methyl diazoacetate with halomethanes. The overall product yields as well as the quantum yield in these reactions are usually low.[1,2] Migita and coworkers provided chemical evidence in support of the nonradical chain mechanism by obtaining different products from the benzoyl peroxide initiated decomposition of ethyl diazoacetate in chloromethanes.[3] On the other hand, Cocivera and Roth argued for a radical chain mechanism originally proposed by Urry and coworkers[4] by showing that the CIDNP emission signal for the α-proton of methyl 2,3,3,3-tetrachloropropionate (1) formed on photolysis of methyl diazo-

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Communications to the Editor